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Division of Biochemistry

– Chemical Biology –

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Fudan University, China, P.R., 21 July–9 August

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VNU University of Science, Vietnam National University, Vietnam, 25 November–20 December

Scope of Research

Chemical biology is an interdisciplinary field of study that is often defined as “chemistry-initiated biology.” As biological processes all stem from chemical events, it should be possible to understand or manipulate biological events using chemistry. Our laboratory has been discovering or designing unique organic molecules that modulate fundamental processes in human cells. Such synthetic organic molecules often serve as tools for basic cell biology. Discovery or design of small molecules with unique biological activities permits small-molecule-initiated exploration of complex cellular events. Our mission is to create a new world of bioactive synthetic molecules: new modes of activity, new shapes, and new sizes. We hope to open new avenues for small-molecule applications in a range of fields, including future concepts in drug discovery and use of small molecules for cell therapy.

KEYWORDS

Cell Therapy

Chemical Library

Chemical Biology

Chemical Genetics

Small Molecules

Selected Publications

Perron, A.; Nishikawa, Y.; Iwata, J.; Shimojo, H.; Takaya, J.; Kobayashi, K.; Imayoshi, I.; Mbenza, N. M.; Takenoya, M.; Kageyama, R.; Kodama, Y.; Uesugi, M., Small-molecule Screening Yields a Compound That Inhibits the Cancer-associated Transcription Factor Hes1 via the PHB2 Chaperone, *J Biol. Chem.*, **293**, 8285-8294 (2018).

Yatsuzuka, K.; Sato, S.; Pe, K. B.; Katsuda, Y.; Takashima, I.; Watanabe, M.; Uesugi, M., Live-cell Imaging of Multiple Endogenous mRNAs Permits the Direct Observation of RNA Granule Dynamics, *Chem. Commun.*, **54**, 7151-7154 (2018).

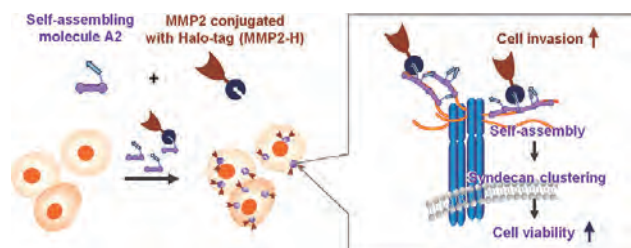
Furuta, T.; Mizukami, Y.; Asano, L.; Kotake, K.; Ziegler, S.; Yoshida, H.; Watanabe, M.; Sato, S.; Waldmann, H.; Nishikawa, M.; Uesugi, M., Nutrient-Based Chemical Library as a Source of Energy Metabolism Modulators, *ACS Chem. Biol.*, **14**, 1860-1865 (2019).

Takashima, I.; Kusamori, K.; Hakariya, H.; Takashima, M.; Vu, T. H.; Mizukami, Y.; Noda, N.; Takayama, Y.; Katsuda, Y.; Sato, S.; Takakura, Y.; Nishikawa, M.; Uesugi, M., Multifunctionalization of Cells with a Self-Assembling Molecule to Enhance Cell Engraftment, *ACS Chem. Biol.*, **14**, 775-783 (2019).

Nagata, A.; Akagi, Y.; Asano, L.; Kotake, K.; Kawagoe, F.; Mendoza, A.; Masoud, S. S.; Usuda, K.; Yasui, K.; Takemoto, Y.; Kittaka, A.; Nagasawa, K.; Uesugi, M., Synthetic Chemical Probes That Dissect Vitamin D Activities, *ACS Chem. Biol.*, **14**, 2851-2858 (2019).

Multifunctionalization of Cells with a Self-Assembling Molecule to Enhance Cell Engraftment

Cell-based therapy is a promising approach to restoring lost functions to compromised organs. However, the issue of inefficient cell engraftment remains to be resolved. Herein, we take a chemical approach to facilitate cell engraftment by using self-assembling molecules which modify two cellular traits: cell survival and invasiveness. In this system, the self-assembling molecule induces syndecan-4 clusters on the cellular surface, leading to enhanced cell viability. Further integration with Halo-tag technology provided this self-assembly structure with matrix metalloproteinase-2 to functionalize cells with cell-invasion activity. In vivo experiments showed that the pretreated cells were able to survive injection and then penetrate and engraft into the host tissue, demonstrating that the system enhances cell engraftment. Therefore, cell-surface modification via an alliance between self-assembling molecules and ligation technologies may prove to be a promising method for cell engraftment.



Nutrient-Based Chemical Library as a Source of Energy Metabolism Modulators

Covalent conjugates of multiple nutrients often exhibit greater biological activities than each individual nutrient and more predictable safety profiles than completely unnatural chemical entities. Here, we report the construction and application of a focused chemical library of 308 covalent conjugates of a variety of small-molecule nutrients. Screening of the library with a reporter gene of sterol reg-

ulatory element-binding protein (SREBP), a master regulator of mammalian lipogenesis, led to the discovery of a conjugate of docosahexaenoic acid (DHA), glucosamine, and amino acids as an inhibitor of SREBP (molecule 1, DHG). Mechanistic analyses indicate that molecule 1 impairs the SREBP activity by inhibiting glucose transporters and thereby activating AMP-activated protein kinase (AMPK). Oral administration of molecule 1 suppressed the intestinal absorption of glucose in mice. These results suggest that such synthetic libraries of nutrient conjugates serve as a source of novel chemical tools and pharmaceutical seeds that modulate energy metabolism.

